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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/500,904	02/09/00	HARLEY J	OMRF 161 CIP

HM12/1228

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EXAMINER	
FOLEY,S	
ART UNIT	**PAPER NUMBER**
1648	7

DATE MAILED: 12/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/500,904	HARLEY ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 1-5,11-18 and 23-26 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-10 and 19-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims 1-26 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☒ Other: *Notice of Sequence Compliance* .

DETAILED ACTION

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Specification

The disclosure is objected to because of the following informalities: pages 38, 44, and 53 are blank. In addition, page 62 has a table that has been glued into the specification. A replacement page is required containing the same information accompanied by an assurance that there contains no new matter.

Appropriate correction is required.

Information Disclosure Statement

The information disclosure statement filed 4/20/00 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. A few of the references were missing and were not considered. The Qualtierre and Pearson reference from Virology Vol. 102, pages 360-369 was missing the first 3 pages.

Drawings

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. There are descriptions of drawings on pages 9-12, but no drawings to accompany the descriptions. Applicant is required to furnish drawings under 37 CFR 1.81. No new matter may be introduced in the required drawings.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 11-18, drawn to a vaccine, classified in class 424, subclass 230.1.

II. Claims 6-10, 19-22, drawn to a diagnostic test, classified in class 435, subclass 5.

III. Claims 23-25, drawn to an in vivo screening method for therapeutics, classified in class 424, subclass 9.2.

IV. Claim 26, drawn to a method of screening risk factors, classified in class 435, subclass 6.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are patentably distinct for the following reasons: The methods of inventions I-IV have different ultimate goals which require the use of different products to achieve the goals and the use of different method steps to reach the ultimate goal of the method.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Patrea Pabst on 11/30/00, a provisional election was made without traverse to prosecute the invention of Group II, claims 6-10 and 19-22. Affirmation of this election must be made by applicant in replying to this Office action. Claims

1-5, 11-18, and 23-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 8 and 20 are objected to because of the following informalities: grammatical errors. The claims should recite "wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of..." Appropriate correction is required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) and must include the status in that application. In addition, there was no claim to priority to all of the parents in the oath. Therefore, the priority date for this application has been determined to be 1/13/97, from parent application 08/781296, which was the only application claimed in the fist line of the specification and in the oath.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6-10 and 19-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 35 of copending Application No. 08/781,296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim in the parent is directed to a composition comprising the same peptide molecules (SEQ ID 1-3, 7, 26, 27, 33, 34, 37, and 38 in the diagnostic kit in claims 8 and 21 of the instant application. The two applications are claiming the same uses for the peptides, that is, identifying the likelihood that someone will develop autoimmune disease.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-10 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-10 and 19-22 are directed to determining the "likelihood" whether an individual is "at risk" for developing an autoimmune disease based on control samples from patients who are "not at risk" for developing an autoimmune disease. "Likelihood" and "at risk" are relative terms which render the claims indefinite. The term "likelihood" and "at risk" are not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The risk factors to be assessed in the diagnostic tests in the determining a concrete statistical value correlating to the chance of a subject contracting an autoimmune disease and with the actual diagnosis of the autoimmune disease has not been established. This fact is clearly illustrated in claim 19, affecting all dependent claims 20-22. The claim is drawn to comparing sample analysis of the control group without autoimmune disease to test samples to "determine **if** the differences in levels" indicate a higher or lower risk of developing autoimmune disease. This claim clearly states that the diagnostic test has not been proven to indicate the autoimmune status of an individual.

Claims 8 and 21 are indefinite because it recites an improper Markush group. The applicant is referred to MPEP 2173.05(h) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A, B, C **and** D" or "wherein R is A, B, C **or** D".

Claims 7 and 20 are vague and indefinite. The claims are drawn to a diagnostic test kit "where the reagents are used in assays based upon the relative presence of an antibody" etc. Are

different reagents used based on the level of antibody present? The claim is confusing because it seems to be drawn to using one set of reagents for low antibody level and another set of reagents for a high antibody level. How would one predict what the antibody level was to correctly select the appropriate reagent?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-10, 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of determining the likelihood that an individual has an autoimmune disorder induced by Epstein-Barr Virus (EBV), or is at risk for developing an autoimmune disorder or lupus. This assay would determine the relative presence of antibody levels to certain peptides derived from EBV. It is clear from the language in the claims that the assay has not been determined to indicate the immune status of an individual, see the reasoning above. The specification has pointed out cross-reactivities to antibodies derived from EBV and lupus, such as anti-Sm and Epstein-Barr Virus nuclear antigen-1 (EBNA-1), that the applicants have concluded to be the "probable cause of lupus" on page 12, also see example 1. Although the application clearly demonstrates cross-reactivity with specific peptides between EBV and lupus, the assumption that EBV causes lupus or any other autoimmune disease is inconclusive. There is not conclusive evidence presented that clearly indicates lupus is caused by the direct

result of exposure to EBV. The specification states that one peptide, SEQ ID 7, is a major epitope found in patients that had mononucleosis, but is not bound by patients with lupus, see page 56. The epitope obviously has the ability to present itself in the immune system indicating that if EBV was present, the epitope would be detected, regardless of what symptoms were presented. Therefore, there must be other unidentified factors that lead to autoimmune disease, making the determination of "likelihood" of development impossible to predict.

The state of the art at the time of the invention also recognizes cross-reactivity of some peptides related to EBV and autoimmune disease, but no one has shown the correlation of EBV developing into autoimmune disease by Koch's Postulates. One skilled in the art would have reason to doubt that EBV causes autoimmune disease. Individuals diagnosed with autoimmune disease and then are exposed to EBV may prove lethal, but normal individuals have mild symptoms or are asymptomatic, see White et al. page 154, last paragraph and page 343-344. Carson teaches that there are many obstacles for predicting autoimmune disease. Family and population studies indicate that several genes can increase susceptibility of autoimmune disease or influence immune responses to infectious agents that may trigger autoimmunity. Because of the somatic generation of immune diversity, genetically identical individuals have different immune systems, indicating the difficulty in predicting the outcome of a changing environment, see the abstract. Therefore, due to the lack of direction or examples conclusively correlating evidence that EBV causes autoimmune disease, the state of the art and the lack of predictability by one skilled in the art to determine the probability of development of autoimmune disease, there would be an undue amount of experimentation required of one skilled in the art to practice

the invention. Therefore the scope of the invention is limited to a diagnostic test to determine levels of antibodies to EBV and lupus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 7, 10, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rhodes et al.

The claims are drawn to a diagnostic test to detect levels of antibodies to Epstein-Barr Virus and lupus against normal individuals.

Rhodes et al. teaches that individuals diagnosed with mononucleosis develop antibodies against Epstein-Barr Virus nuclear antigen (EBNA). The EBNA contains a unique glycine-alanine repeating sequence. Rhodes et al. synthesized peptides corresponding to various regions of the EBNA molecule within or near this sequence. The sera of individuals with antibodies against EBV contained abundant antibodies also reactive with several of the synthetic peptides. When compared with normal controls, antibody levels to the glycine-alanine peptides were significantly higher in patients with rheumatoid arthritis and progressive systemic sclerosis, but not in patients with two other autoimmune disorders, which included lupus. The teachings of Rhodes et al. teach that antibodies against this peptide detect the EBNA protein and that humans infected with EBV produce high titers of antibodies reactive to these synthetic antigens and antibody titers against the peptides are abnormally elevated in certain autoimmune diseases.

Lupus patients were found to have an elevation in P60 and P27 as compared with the normal controls. See the abstract and table 1. Thus, the teachings of Rhodes anticipate claims 6, 7, and 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-10 and 19-22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Petersen et al.

The claims are drawn to a diagnostic test to detect levels of antibodies to specific peptides derived from EBNA from to detect Epstein-Barr Virus and lupus against normal individual control samples.

Petersen et al. teaches a panel of peptides derived from EBNA-1 that cross react with antibodies from patients with rheumatoid arthritis (RA) patients and patients with lupus against normal controls. Petersen et al. teaches that the sera from RA patients and that from the lupus patients contained elevated levels of IgG antibodies to 2 non-glysine alanine peptides and 3 non-glysine peptides respectively. Two of the 3 peptides are glysine rich, but are distinct from each other, see the abstract. The antibody reactivity in RA and lupus patients was significantly elevated in E4 and E11. Additionally, the antibodies from E14 were significantly elevated in lupus patients, see figures 2 and 3 on pages 995 and 996. However, there was no correlation between antibody responses between the peptides in the different subgroups of patients,

indicating that the epitopes represented by the various peptides are discrete. The E4 peptide shares a high homology to SEQ ID NO: 102 in the application by only 2 amino acids in length. Petersen et al. identified epitopes that distinguish RA patients, convalescent mononucleosis patients, and lupus patients based on the cross-reactivity of the peptides using ELISA. The peptides derived from EBNA-1 in the application are centered on the peptide derivatives taught by Petersen et al. For example, SEQ ID NO: 100 is contained in the E3 peptide taught by Petersen et al. and SEQ ID 37 shares a high homology to E14, minus 3 amino acids. SEQ ID 38 has matches the C terminal half of E14 and the N terminal half of E11, while SEQ ID NO: 107 overlaps 38 in the E11 portion and ends with the C terminal half of E11. Therefore, the teachings of Petersen et al. anticipate the peptide derivations in the application. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the peptide derivatives disclosed by Petersen et al. to further differentiate the epitopes between the different subject populations.

The glycine-alanine rich peptide, P62, was reactive in RA patients and convalescent mononucleosis patients, but had no cross-reactivity with host proteins, see the second paragraph on page 994 and figure 5 on page 997. It would have been obvious to one of ordinary skill in the art at the time the invention was made that this teaching of Petersen et al. would not have any cross-reactivity in lupus patients because of the systemic autoimmune reactions observed in these patients. From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation in producing the claimed invention because of the clear difference in epitope specificity in each group of patients. Therefore, the invention as a whole is

prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 8, 9, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhodes et al.

The claims are drawn to a diagnostic test used to detect antibodies to peptides from EBV selected from a list of specific peptides in the claims.

See the teachings of Rhodes et al. above. Rhodes et al does not teach the specific peptides in the claims. However, Rhodes et al. identified a number of peptides that cross-react with EBV and autoimmune disorders and in addition to teaching that glycine-alanine rich peptides do not react with patients sera diagnosed with lupus. All of the peptides taught by Rhodes et al. were peptides that were derive from EBNA. All of the specific peptides claimed in claims 7 and 8 are also derived from EBNA. Even though the Rhodes et al. does not teach the specific peptides in the claims, the teachings demonstrate that it would have been obvious for one of ordinary skill in the art at the time the invention was made to use peptide derivatives to determine the antibody response in EBV infected individuals and those with an immune disorder since the peptides from EBNA cross-react with both groups of subjects. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
December 26, 2000

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1600